ALINEA

NUTRITION

APRIL 2022

www.alineanutrition.com

TABLE OF

# CONTENTS

**Applegate CC, Rowles JL, Ranard KM, Jeon S, Erdman JW. Soy Consumption and the Risk of Prostate Cancer: An Updated Systematic Review and Meta-Analysis. Nutrients. 2018;10(1):40.**

## What We Know, Think We Know, or Are Starting to Know

One could argue that when it comes to diet and cancer, much of our focus tends to fall on colorectal and breast cancers, respectively. There are sex-specific considerations for these respective cancers, as men exhibit a higher risk for colorectal cancer, while breast cancer affects almost exclusively women [(1)].

However, prostate cancer [PCa] is the second-most common cancer in men, and with a high mortality rate [(1)]. Similar to what is observed in the epidemiology of breast cancer, the incidence and mortality rates for PCa differ substantially between regions of the world, with populations in East Asia exhibiting significantly lower rates of PCa compared to Western populations [(1)].

From a preventative nutrition perspective, lycopene – a carotenoid found in high concentrations in tomatoes – has arguably attracted most interest regarding PCa [(2)]. Yet again, however, a similar theme between breast cancer and PCa emerges insofar as the regional differences in risk for both cancers have led researchers to set their sights on a particular food group: soy.

Soy foods are rich in a specific type of (poly)phenol compounds known as isoflavones, particularly genistein and daidzein. Daidzein is also metabolised by gut bacteria to produce equol, which appears to be responsible for much of the benefits associated with dietary daidzein intake [(3)]. These compounds exert anti-carcinogenic activity which may be relevant for PCa*. The present study investigated associations between soy foods and soy isoflavones on PCa risk.

## *Geek Box: Soy Isoflavones and Prostate Cancer

*Before they can be fully absorbed, soy isoflavones are metabolised by gut bacteria; this is a step that is now recognised as a critical stage in metabolism and ultimate bioactivity of all (poly) phenol compounds. While genistein exerts biological activity, the activity of daidzein may rely on conversion to equol. Equal is exclusively a product of bacterial metabolism of daidzein and does not appear in the body unless soy foods are produced in the diet. One potential mechanism through which soy isoflavones and equol may lower PCa risk is through the oestrogen-receptor beta [ER-ß]. Of the two oestrogen-receptors, ER-alpha induces cell hyper-proliferation, a fancy term for the rapid growth and replication of cells that is an important characteristic of cancers. In contrast, ER-ß counter acts this process, and both genistein and equol display a high affinity for binding to the ER-ß, which may suppress cell growth. Importantly for PCa, ER-ß is present in the prostate gland. Another potential role for equol is in relation to the androgen, DHT, as high circulating levels of DHT appear to stimulate the growth of cancerous cells in the prostate. Equol has been shown to bind to DHT, thus preventing it from binding to androgen-receptors in the prostate. Genistein may also inhibit the production of prostate-specific antigen [PSA], an androgen-dependent gene. It is important to note that each of the mechanisms identified for soy isoflavones and equol in the prostate that influence the androgen-receptor pathways are independent of actual effects on male sex hormone production, e.g., testosterone. Despite the urban myths, and despite my thorough enjoyment of winding up the plant-based crowd with soy-related tropes, soy consumption has no adverse effects on testosterone levels. It is important to note that the potential mechanisms outlined above are derived from either animal models or in vitro studies, so we must be cautious not to over-extrapolate. However, such evidence is useful in considering the biological plausibility of associations noted in epidemiology.*

## The Study

The researchers conducted a meta-analysis of studies on soy intake and PCa risk, with the following inclusion criteria for the primary studies:

- The study design was a randomized control trial, prospective cohort study, cross-sectional study, retrospective study, or case-control study;
- The study examined the association between soy foods and/or isoflavones from diet and/or measured circulating levels of isoflavones;
- The study reported relative risk with 95% confidence intervals.

PubMed, Web of Science, and the Cochrane Library were searched to identify relevant published articles. Study quality was determined using the Newcastle-Ottawa Scale [NOS], a validated tool to assess the quality of non-randomised trials [scores of 1–3, 4–6 and 7–9, were considered low, medium, and high quality, respectively].

The relative risks and 95% CI were calculated from the primary studies from the comparison of highest vs. lowest intakes. For fermented soy foods, the analysis included foods such as soy milk, tofu, and soybeans. Fermented soy foods included miso soup and natto.

**Results:** A total of 30 primary studies were included, totalling 266,699 participants and 21,612 total cases of PCa. 12 studies were from Asia, 10 from North America, and 8 from Europe. Studies were scored either medium or high quality according to the NOS. The following are the outcomes investigated with the number of studies in parentheses.

- ***Total Soy Foods [n = 16]*:** There was a significant 29% [RR 0.71, 95% CI 0.58 – 0.85] lower risk of PCa.
- ***Unfermented Soy Foods [n = 11]*:** There was a significant 35% [RR 0.65, 95% CI 0.56 – 0.83] lower risk of PCa.
- ***Fermented Soy Foods [n = 8]*:** There was no significant association for fermented soy foods, a 14% lower risk and range from 34% lower to 13% higher risk [RR 0.86, 95% CI 0.66 – 1.13], i.e., no clear direction of effect.
- ***Genistein*:** Genistein was measured both from diet [*n* = 10] and circulating levels [*n* = 9]. Dietary genistein was associated with a significant 10% [RR 0.90, 95% CI 0.84 – 0.97] lower PCa risk, while circulating genistein levels were not significantly associated with lower PCa risk [more under ***Interesting Finding***, below].
- ***Daidzein*:** Daidzein was measured both from diet [*n* = 10] and circulating levels [*n* = 7]. Dietary daidzein was associated with a significant 16% [RR 0.84, 95% CI 0.73 – 0.97] lower PCa risk, while circulating daidzein levels were not significantly associated with lower PCa risk [more under ***Interesting Finding***, below].
- ***Advanced PCa Risk*:** For advanced PCa, which is where the cancer has spread from the prostate to other sites, there was no significant effect of total soy foods based on 4 cohort studies [RR 0.87, 95% CI 0.74 – 1.06].

## The Critical Breakdown

**Pros:** The study was the first to drill down and consider the exposure of soy at multiple levels: total soy food intake, unfermented soy, fermented soy, total isoflavones, genistein and daidzein. Further, circulating levels of total isoflavones, genistein and daidzein were also analysed. The overall sample size was large, although this would have provided most statistically power to the total soy foods outcome with 16 studies. There was also a large number of cases of PCa in the studies.

**Cons:** The pet-peeve of nutrition meta-analyses: "distortive lumping", i.e., the combining of a wide variety of study designs and exposures into an overall analysis. Most included studies [*n* = 15] were case-control studies, reflecting a limitation of the epidemiology of diet and PCa risk which is the overall lack of prospective studies investigating these associations over time [more under ***Key Characteristic***, below]. As usual [yawn], the researchers did not do any subgroup analysis of how "high" or "low" in actual intakes was associated with the various outcomes, which is frustrating given that there were regional differences shown in the analysis for some outcomes. There was high heterogeneity between the studies, indicating wide variation between the included studies, a statistical reflection of the distortive lumping of studies together.

## Key Characteristic

Let's recap on the difference between a case-control and prospective cohort study. In a case-control design, several healthy participants are selected as controls for each case of a disease that has diagnosed, e.g., PCa. In this design, the researchers identify cases of PCa that have *already occurred*, or as they occur if the parent study is a prospective cohort, and then select up to 4 to 5 healthy controls to match with a case of PCa. The case-control study would then compare, for example, dietary intake of soy or circulating isoflavone levels in the healthy controls vs. the PCa cases.

Prospective cohort studies take a cohort of people from the population, and follow them prospectively, i.e., over time. The advantage to this design is that exposures such as diet, smoking, family history, etc., can be assessed *before* a disease develops in the participants. This reduces the potential for recall bias, selection bias, and other biases which other observational designs – like case-control or retrospective studies – are more prone to. Another advantage of prospective cohort studies is the potential sample size, which can range into the thousands to hundreds of thousands of participants, thus providing more power to detect effects and minimise the influence of measurement error from smaller sample sizes, i.e., the results may be more accurate.

With these differences in design in mind, it is important to now consider that there was quite a large difference in the magnitudes of effect observed from both designs in the present study. Specifically, case-control studies showed a 39% relative risk reduction compared to just 10% from prospective cohorts. Whatever the potential pitfalls of nutritional epidemiology, prospective cohorts remain the design that is strongest, eliminating the potential for recall bias and, importantly, recruiting participants *before* they have any observable or diagnosed disease.

Such a difference in the risk estimates is too big to ignore, and the higher methodological rigour of prospective studies suggests that the case-control studies may be generating exaggerated effect sizes. This is a major, and recognised, limitation of the diet and PCa literature; there are a lack of prospective studies investigating these associations over the longer-term [3]. The differences in the magnitude of effect between these two study designs from the present meta-analysis invites caution in interpreting where the 'true' effect may lie, and more prospective studies would be better suited to determining this discrepancy.

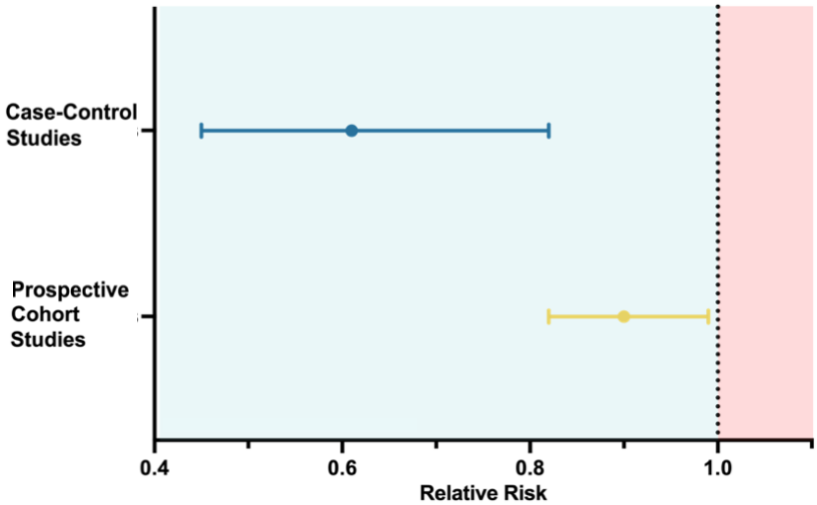


***Figure** illustrating the difference in relative risk between case-control studies and prospective cohort studies. The magnitude of effect observed in prospective studies is substantially more modest and brushing shoulders with the 1.0. The true effect may certainly lie in this magnitude of lower risk associated with soy foods; however, it is clear from the 95% CI derived from case-control studies that this is quite an imprecise estimate of effect. Design is important, and that includes for epidemiology!*

## Interesting Finding

Although *dietary* genistein and daidzein were associated with lower PCa risk, *circulating* levels [i.e., levels measured in blood] of genistein and daidzein were not. Now, you could think this is an inconsistency; why would intake from diet show different associations to levels in the body? And would this type of finding indicate a flaw in the study's findings?

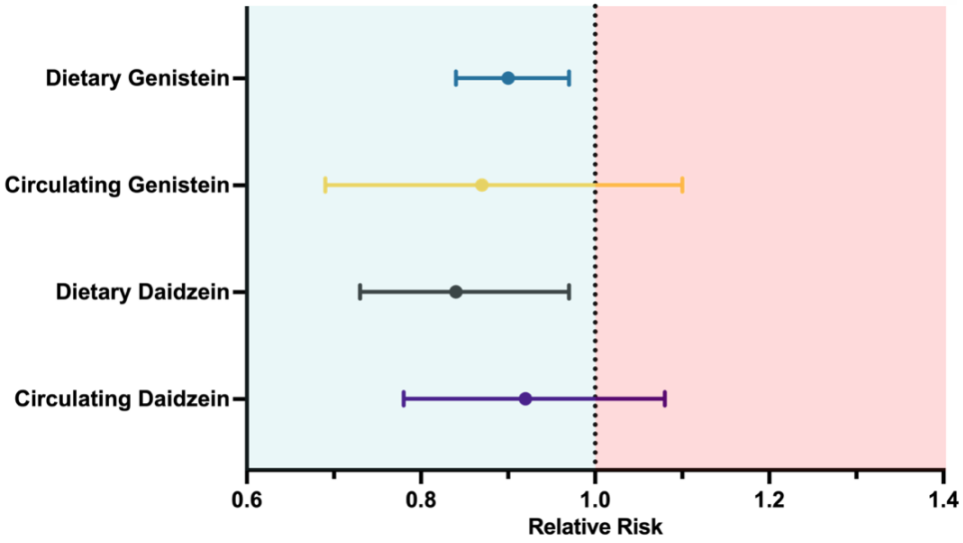


***Figure** illustrating the relative risk [**circle in each line**] with 95% confidence intervals [**arms of each line**] for the soy isoflavones genistein and daidzein from both dietary assessment and circulating measurements. Genistein and daidzein from diet were calculated based on the levels of each isoflavone in soy foods reported in dietary assessments [mostly food-frequency questionnaires]. Circulating genistein and daidzein were measured mostly in plasma [6 studies] and in serum [3 studies].*

The first thing to remember is that dietary and circulating levels of any nutrient in the body are *measuring different things*. Diet is generally measured using a food-frequency questionnaire or other question-based assessment e.g., 24 h recall. Circulating levels are measured by taking blood samples and analysing levels of the nutrient or bioactive compound in question in a laboratory. The mistake to avoid making is assuming that there is a straight line between dietary intake and levels in the body.

This is because any nutrient or bioactive compound undergoes digestion, absorption, metabolism, and assimilation into different tissue compartments. For (poly)phenol compounds such as soy isoflavones, there is an added complication in that these compounds are treated differently by the body because they are *not* nutrients [e.g., a vitamin or mineral]. These compounds, isoflavones included, undergo extensive metabolism by bacteria in the colon, and it is the metabolites that are absorbed and exert biological activity [(4)].

For soy isoflavones, the composition of bacteria in the gut appears to be crucial in determining the level of conversion of these isoflavones to bioactive metabolites, and this appears to differ based on background diet and genetics [(3)]. An analysis of circulating plasma biomarkers of soy isoflavones indicated substantial variation between individuals of 30-96% [(5)]. Arguably, plasma measurements of soy isoflavones are not an effective biomarker to relate *dietary intake* of isoflavones to disease risk.

For your own further learning on the ***Interesting Finding***, above, if you have yet to watch the Research Lecture on biomarkers of dietary intake, I encourage you to do so.

## Relevance

Ok, let' s try to put this all in some context. Starting with the outcome of total soy foods, there was a 29% [range of 15% to 42%] lower risk of PCa. However, as half of the 16 included studies for this outcome were case-control studies, both the magnitude of effect [i.e., 29% relative risk reduction] and the precision of the estimate [15% to 42% lower] may have been influenced disproportionately by case-control studies [for reasons discussed under Key Characteristic, above].

Nevertheless, there does appear to be a signal from the noise in relation to total dietary soy intake, and in relation to dietary intakes of the primary soy isoflavones, genistein and daidzein, with a lower risk of PCa [3,6].

Randomised controlled trials to date have largely been unhelpful in resolving where the benefit may lie, and suffer from numerous design flaws common to nutrition interventions: dose of isoflavones [too low], duration of intervention relative to the time-course of PCa progression [too short], and confounding with administering other nutrients – vitamin E and selenium – that potentially influence PCa risk [3,6].

In relation to the time-course of disease, the lack of association for lower risk of advanced PCa in the present study is also instructive. PCa has a very long latency period of >10 years, i.e., the period during which the disease is progressing but not yet clinically manifested and diagnosable. It may be that soy and isoflavones exert effects more prophylactically, lowering risk of progression from early stages to advanced. This would suggest that intake earlier in life is influencing PCa risk over the lifespan; the precise reason why more prospective studies are required.

## Application to Practice

It would be remiss in all this discussion on dietary factors not to mention that health inequalities are a major issue PCa, with a disproportionate burden of disease in Black men of West African ancestry, particularly in the U.S., UK, and Caribbean [7]. The genetic predispositions are exacerbated by socio-economic determinants of health, such as health access, access to physical activity, and access to good nutrition [8].

The jury remains in deliberation over the contribution of specific nutrients and bioactive food components of interest for PCa, in particular lycopene and soy isoflavones. Yet the evidence to date suggests that both compounds may, at levels obtainable through dietary intake and through plausible biological mechanisms, lower risk of progression of PCa. For soy isoflavones specifically, we do need more prospective studies and better designed RCTs to help determine how relevant the potential preventative effect of soy foods on PCa are.

## References


1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68(6):394–424.
2. Chen P, Zhang W, Wang X, Zhao K, Negi DS, Zhuo L, et al. Lycopene and risk of prostate cancer. Medicine. 2015;94(33):e1260.
3. Messina M. Soy and Health Update: Evaluation of the Clinical and Epidemiologic Literature. Nutrients. 2016;8(12):754.
4. del Rio D, Rodriguez-Mateos A, Spencer JPE, Tognolini M, Borges G, Crozier A. Dietary (Poly) phenolics in Human Health: Structures, Bioavailability, and Evidence of Protective Effects Against Chronic Diseases. Antioxidants & Redox Signaling. 2013;18(14):1818–92.
5. van der Velpen V, Hollman PC, van Nielen M, Schouten EG, Mensink M, van' t Veer P, et al. Large inter-individual variation in isoflavone plasma concentration limits use of isoflavone intake data for risk assessment. European Journal of Clinical Nutrition. 2014;68(10):1141–7.
6. Sivoňova M, Kaplan P, Tatarkova Z, Lichardusova L, Dušenka R, Jurečekova J. Androgen receptor and soy isoflavones in prostate cancer. Molecular and Clinical Oncology. 2018;10:191-204
7. Odedina FT, Akinremi TO, Chinegwundoh F, Roberts R, Yu D, Reams RR, et al. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. Infectious Agents and Cancer. 2009;4(S1):S2.
8. Nelson WG, Brawley OW, Isaacs WB, Platz EA, Yegnasubramanian S, Sfanos KS, et al. Health inequity drives disease biology to create disparities in prostate cancer outcomes. Journal of Clinical Investigation. 2022;132(3):e155031.